

**REMARKS:**

Claims 1, 3, 5, 6 and 8-19 are in the case and presented for consideration.

Claim 1 has been amended to include the subject matter of canceled claim 2 and claim 3 has been amended to improve its form. No new matter has been added.

Applicants thank the Examiner's for the indication that the previous formal and obviousness-type double patenting rejects have been overcome.

Claims 1-3, 5-6, and 8-11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zak et al. (US Patent 6,503,943) (hereafter Zak) in view of Collaueri et al. (US Patent 6,221,393) (hereafter Collaueri) and further in view of Caril et al. (US Patent US 5,275,824) (hereafter Caril) for the reasons made of record in Paper No. 20100707.

In finding the Applicants' previous arguments unpersuasive, the Examiner reasons that the Applicants' argument of individual references under a 35 U.S.C. 103 rejection is found not persuasive and secondly Applicants are asked to note that the claims are drawn to a composition and not a process of making.

In further reply, the Examiner is respectfully requested to consider the following where both the unobviousness of claim 1 from the combination of Zak, Collaueri and Caril that would be made by the person of ordinary skill in the art of this invention, and the relevancy of the process steps in claim 1 are discussed.

Claims 12-19 also stand rejected under 35 U.S.C. 103(a) as being unpatentable over Caril in view of Zak and further in view of Collaueri for the reasons made of record in Paper No. 20100707 and following in the Final Office Action. The Examiner points out that this rejection was not traversed, therefore no response is due.

To avoid any omission of formalities, the Applicants here formally traverse both the Examiner's rejection of claims 1-3, 5-6, and 8-11 based on the combination of Zak, Collaueri and Caril, and the Examiner's rejection of claims 12-19 based on the combination of Caril, Zak and Collaueri.

Since claims 12-19 are method claims and were examined as such, the Examiner's citation of *In re Thorpe*, *In re Marasi*, *Ex parte Gray*, and *In re Best*, cited for the principle that method steps as normally not considered as differences between product-by-process claims and the prior art, would not appear to be relevant to the examination of the method claims. In addition the composition of claims 1-3, 5-6, and 8-11 is not the same as a composition of the same ingredients but make by another process. The use of wet granulation alone increases the moisture content of the resulting composition for example.

The following reasons why the person of ordinary skill in the art of this invention would not combine the teachings of Zak, Collaueri and Caril, or the teachings of Caril, Zak and Collaueri as cited, to reach the claimed invention, are material for all of the claims, not just the composition claims and not just the method claims.

Recasting the Examiner's rejection of product-by-process (composition) claim 1 and method claim 12 as a question:

Is the composition obtained by the wet granulation defined in claim 1 and required by claim 12 of the present application obvious from any composition obtained by the wet granulations according to Zak as combined with Collaueri and as further combined with Carli?

Although it is understood that the Examiner's rejections are based on a combination of the three references, what is actually taught by each reference as a whole must first be considered or else the person of ordinary skill in the art would not know what to combine with what, to reach the sixteen claimed combinations of claims 1, 3, 5, 6 and 8 to 19.

(1) Zak:

Zak does not mention any wet granulation at all so the skilled artisan must look elsewhere for this teaching and combine it with Zak in some way that makes sense for both the other reference and for Zak. Otherwise the combination would not be an obvious one.

(2) Collaueri:

Collaueri does not expressly teach wet granulation either. Table 1 of this reference does not comprise anything which could be related to the wet granulation. The only term "wetting," mentioned in Table 1, concerns "wetting angle" which has nothing to do with wet granulation (please see the Applicants' arguments set forth in the reply to the preceding Action). The Examiner appears to ignore this distinction and continues to insist that:

Table 1 teaches the procedure is by wetting, therefore one of ordinary skill

in the art would necessarily expect that the process is by wet granulation (see col.'s 7 and 8, as required by instant claim 1). (Bottom of page 5 of the Action of Nov. 8, 2010.)

There is no reason at all that “one of ordinary skill in the art would necessarily expect that the process is by wet granulation” as stated. This is an arbitrary finding that has no support in this reference or anywhere else in the prior art.

In addition, and importantly for determining if and how skilled artisan would combine this references with the others, Collaueri pre-granulates the excipients (xanthan gum,...) separately, i.e. without the active ingredient which ingredient is only afterwards mixed with the pre-granulated excipient matrix (see the Applicants' arguments set forth in the reply to the preceding Action). It is thus clear that the structure of the claimed composition must be (a) different and (b) non-obvious from that obtained by Collaueri. Further, in Collaueri: (a) the active ingredient is mostly located on the surface of the Collaueri's pre-granulated excipient matrix rather than homogeneously dissipated in the matrix as it is the case of the claimed composition which is a direct result of the difference in processing (another example of the process causing a different structure in the composition), and (b) for the claimed composition, there was, in advance, no certainty of whether the sensible invention ingredient of formula (II) would be able to face the conditions of the wet granulation at all, since Collaueri's granulation is implemented without the active ingredient and therefore cannot provide the person skilled in this art with any guiding information in this respect.

In addition, the person skilled in the art would not have had any motivation to pass from the Collaueri's granulation without active ingredient to wet granulation with the active ingredient, namely when the risk of the decomposition of the active ingredient by wet

granulation conditions was imminent.

Taking account of the foregoing, the invention in its composition (claims 1, 3, 5 and 8-11) and even more so in its method (claims 12-19) should be regarded as very different and non-obvious from the Collaueri's composition, and what the skilled artisan should take away from Collaueri to combine with Zak and Carli, without using hindsight gleaned by first reading the subject application.

(3) Carli:

Carli mentions wet granulation only as an optional intermediate working step having practically no influence on the arrangement of the active ingredient in the excipient matrix.

The Carli composition is prepared (see the Applicants' arguments set forth in the reply to the preceding Action) using the process including: (1) loading the particles of water-soluble but water-swellaable polymer with the required medicament by either swelling with solution of the medicament followed by drying or by high-energy co-grinding; (2) size-enlarging the medicament-loaded polymer particle by wet or dry granulation; and then (3) suspending such loaded polymer particles in a current of air in a fluidized bed apparatus, spraying them with a solution of the coating polymer and then drying them in the same apparatus or by another method.

At first sight, it must be clear for the person skilled in the art that the structure of the Carli composition formed firstly by loading the particles of water-soluble but water-swellaable polymer with the required medicament by either swelling with solution of the medicament followed by drying or by high-energy co-grinding and then by wet granulating the medicament-loaded polymer particles, must be different from the structure of the claimed composition formed by simply common wet granulating the active ingredient with the

excipients and that this simplified inventive composition could not have been predicted by Carli.

The person skilled in the art would have had no motivation and in fact no reason to extract just the wet granulation step from Carli's somewhat sophisticated sequence of steps and use it separately.

Taking account of the foregoing, the invention composition and method should be regarded as different and non-obvious from the Carli composition and method.

(4) Combining Zak with Collaueri and Carli or Carli with Zak and Collaueri:

Leaving aside the fact that Zak never mentions wet granulation, Collaueri's and Carli's granulations are so different, in terms of their implementations, that the person skilled in the art would not have been able to compile them together to obtain any usable instruction leading to the solution as claimed in the present application in any of claims 1 or 3 or 5 or 6 or 8 to 19 inclusive.

Collaueri and Carli would have provided the person skilled in the art with, in fact, two opposite instructions: Collaueri teaching that granulation must be implemented without active ingredient (probably for protecting the active ingredient) and Carli teaching that granulation must be implemented with active ingredient but under condition that some other steps are implemented as well. Taking all of the teaching of the three references into account (which is all that can be done unless improper hindsight is used), these instruction of the prior art would have urged the person skilled in the art to arrive at the conclusion that the either wet granulation should not be used with an active ingredient per Collaueri, or that wet granulation with the active ingredient would not have been successful without Carli's additional steps.

This simple reasoning requires that if the Applicants proposed the implementation of the granulation with the active ingredient and without the Carli additional steps, this skilled artisan would not be lead to such implementation by Collaueri and Carli in any obvious way contemplated by 25 U.S.C. 103.

In addition, it is not obvious from Collaueri, either, that the neutral saccharide and the polysaccharide can be used in far less amounts (at least 5% and 2%, respectively) in comparison with amounts mentioned by Collaueri.

Taking into account the foregoing, the Applicants sincerely believe that the pharmaceutical composition and method as claimed in all of claims 1, 3, 5, 6 and 8-19, and particularly in claims 1 and 12, is not obvious from the combination Zak, Collaueri and Carli or from the combination Carli, Zak and Collaueri, unless one uses improper hindsight gleaned by first reading the subject application.

In view of the foregoing, Applicants respectfully submit that the invention as claimed is not obvious from the cited references taken in combination and that the application is now in condition for allowance.

If any issues remain that have not been addressed to the Examiner's satisfaction, Applicants invite the Examiner to contact the undersigned attorney by telephone in the interest of reaching a conclusion to the length prosecution of this application.

Favorable action is respectfully requested.

Respectfully submitted,

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Dated: March 3, 2011

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